Ceric Ammonium Nitrate supported on Hy-Zeolite Catalyzed Oxidative Condensation Reaction and its Docking Studies

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ABSTRACT:
The chemistry of chalcone has been recognized as a significant field of study. Chalcone serve as to prepare starting materials for the synthesis of various heterocyclic compounds. From the backbone of reported literature, we have developed an alternative heterogeneous and simple catalytic system for the synthesis of chalcones via the oxidative condensation of benzyl alcohol with substituted acetophenone using metal nitrate supported HY-Zeolite as a catalyst. 30 mol% CAN supported HY-zeolite has been efficiently used as a catalyst for the oxidative condensation reaction of benzyl alcohol with substituted acetophenones in the presence of hydrogen peroxide as an oxidant in toluene to afford the corresponding chalcones in good to moderate yields. Docking studies were carried out for the synthesized compounds towards the protein Lysine aminotransferase using the software.

KEYWORDS: Chalcone, synthesis, CAN Supported HY-zeolite, Docking studies.

INTRODUCTION:

In organic chemistry the reusable catalyst plays an important role to increase the environmental awareness as well as focusing to initiate green chemistry[1]. In particular, the oxidation of alcohols to their carbonyl products achieved by using noble metal catalysts is the more significant fundamental reaction in both the cosmetic and pharmaceutical industries[2-6]. Conversion of alcohol to aldehyde is an important organic transformation reaction particularly benzyl alcohol to benzaldehyde. Benzaldehyde is a valuable chemical in various industries[7]. In industry chromate or permanganate were used as an oxidant which are expensive and environmentally unfriendly[8].

Due to this there is a concern in finding out different methods that are both reasonably efficient and more eco-friendly. Use of molecular oxygen generates or hydrogen peroxide in the presence of a transition metal compound as catalyst[9] is the possible solution. In the case of catalytic oxygen-transfer reactions use hydrogen peroxide as an oxygen donor is the preferred solution[10-13].

Various reagents have been used to converting alcohol to corresponding aldehydes. Lead tetra acetate, manganese dioxide and permanganate have also been used as oxidizing agents for the oxidation of benzyl alcohol, also use of dichromate in aqueous sulfuric acid, glacial acetic acid, or aqueous acetic acid often leads to further oxidation of the aldehyde[14]. Oxidations done by oxides of ruthenium, selenium, nickels and dinitrogen tetroxide are too inconvenient, expensive, or toxic to use routinely[15]. The catalytic method using a stoichiometric amount of inorganic salts and transition metal complexes as catalysts are new pathway has been developed to overcome these disadvantages[16-17]. There are many problem arises during the homogeneous catalytic processes which can be resolved by heterogeneous alternatives. Due to their unique surface electronic properties a number of heterogeneous catalytic systems show good catalytic performance such as, Zn/Alhydrotalcite, Cu_2O, Cu/Zn alloy, Sb_2O_3, $FeCl_3/SiO_2$, $CuFe_2O_4$, $BaWO_4$, ZnS, natural natrolite and CoY zeolite, have been reported to[18-22]. Zeolites can also serve as oxidation catalysts, often other metals have been introduced into the framework. These solid acid catalysts play a prominent role in organic synthesis under heterogeneous conditions. From the backbone of reported literature, we have developed an alternative heterogeneous and simple catalytic system for the synthesis of chalcones via the

oxidative condensation of benzyl alcohol with substituted acetophenone using metal nitrate supported HY-Zeolite as a catalyst.

The reagents used for the synthesis were commercially available and were freshly used after being purified by standard procedures. The reactions were performed by using RB flask. Silica gel coated TLC plates used to monitor the reaction (ethyl acetate/hexane). Electro thermal apparatus used for measuring melting point. NMR spectra were recorded on a FT-NMR Bruker Spectro Spin DRX-300 MHz instrument as DMSO-d_6 solution and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. The synthesised compounds were purified by using common solvents.

MATERIALS AND METHOD:

Materials:

List of chemicals used and their sources are shown below,

Chemicals	Suppliers	Chemicals	Suppliers
Benzyl alcohol	Loba chem	Chloroform	Loba chem
Ferric Nitrate	Loba chem	Hexane	Loba chem
Copper Nitrate	Loba chem	Ethyl acetate	Loba chem
Nickel Nitrate	Loba chem	Acetone	Merck
Cobalt nitrate	Loba chem	Ethanol	Loba chem
Ammonium Ceric Nitrate	Loba chem	Methanol	Loba chem
Acetophenone	Loba chem	Cadmium nitrate	Loba chem
Zinc nitrate	Loba chem	Silica gel-G	Loba chem

Experimental:

A mixture of benzyl alcohol (1.2 equiv) and substituted acetophenone (1 equiv) were added to 0.5g of 30mol% CAN supported HY-zeolite in toluene and hydrogen peroxide as an oxidant. Then the reaction mixture was refluxed at 110°C for specified time. The progress of the reaction was monitored by TLC. After completion of the reaction the catalyst was removed by simple filtration and the filtrate was extracted twice with chloroforn. The combined organic layer was finally washed with water and dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from hot ethanol to obtain pure chalcone derivatives. All the synthesized compounds are known compounds and their spectral data and physical properties are identical with those reported in literature and also compared the same with the synthesised compound.

Computational details and Protein Preparation Process:

The insilico analysis of the synthesized compounds was carried out in the software AUTODOCK 4.2.6 with windows 10 operating system with the Intel processor and 2GB of RAM. The AutoDock 4.2.6 software is based on the principle of Lamarckian genetic algorithm. Initially, the protein was retrived from the Protein Data Bank PDB ID: 2CJD and the protein morphological were studied[23,24]. Further the files were downloaded and the chains were selected. The bonding orders and the charges were added and the hydrogen atoms were added to all the atoms in the selected chain of the protein. The water molecules in chain have been removed in order to prevent it from interaction with the ligand. The initial preparation of the protein molecule is saved in.pdb format for further preparation and energy minimization process of the protein. The active site of the protein was validated and the rectangular box surrounding the active site was located and the grid was generated. Once the grid generation has been made, the RMSD value of the prepared protein molecule and the original molecule was generated[25].

Docking studies and ligand interaction visualization:

Docking studies were carried out for the synthesized compounds towards the protein Lysine amino transferase using the software to identify the binding interactions of the reference molecule and the synthesized molecule to the target protein molecule of the interest[26,27]. Once the doc files of the synthesized molecules were performed by the software, the ligand interaction is visualized using Discovery Studio Visualizer 3.1 developed by Accelrys. The main scope of this software includes structure-based design, simulations, ligand design, macromolecule engineering, macromolecule design and validation (tools for antibody design & optimization, protein-protein docking), and pharmacophore modeling[28-30]. It generates 2D and 3D structures to visualize and analyze the ligand-protein interaction patterns between them.

Preparation of ligands:
The synthesized compounds were processed for Lipinski filters for drug like property. All the structures were prepared to expand protonation and tautomeric states at 7.0±2.0 pH units and conformational sampling was also performed for the synthesized compounds.

RESULTS AND DISCUSSIONS:

The synthesized compounds were further to study about the structure activity relationship the co-crystallized structure with the substrate lysine and ketoglutarate. The crystal structure of the protein was retrieved from the Protein data bank, PDB ID: 2CJD and the reference ligand were analyzed for its polar and non-polar interaction[31, 32]. The reference ligand was prepared and the water molecules were added. After minimization process, the active site of the protein was checked and the rectangular box with a size of 20A° was created. The binding analysis and the ligand interaction with protein were depicted in Figure 1. The docking score and the ligand interactions for the compounds were tabulated in Table 1.

Binding analysis and the ligand interaction of the reference ligand:
The binding analysis of the reference ligand shows that the compound is showing hydrogen bonding interactions with Gly128, Gln274, Glu238 and Glu243. The carbonyl group of the compound revealed a positive interaction with Asp271 and the carboxyl group shows the interaction with Gly242. The docking score of the compound is tabulated in the table 1. The ligand interaction and the binding analysis of the compound is depicted in the figure 1.

Figure 1. The binding analysis and the ligand interaction of the reference ligand

Binding analysis and the ligand interaction of the compound 1-(4-hydroxyphenyl)-3-phenyl-1-propenone:
The binding pattern and the ligand interaction is shown in the figure 2. The compound is found to have four hydrogen bonding interaction with the aminoacids Gly242, Glu243, Asp271 and Thr275. The compound has bulky group interaction with the aminoacid Phe167 and the positive interaction with the aminoacid Glu238. When compared with reference ligand this molecule has good interaction with the active site of the protein when compared to the reference ligand molecule.

Figure 2: The binding analysis and the ligand interaction of the compound 1-(4-hydroxyphenyl)-3-phenyl-1-propenone

Figure. 3: The binding analysis and the ligand interaction of the compound 1-(4-nitrophenyl)-3-phenyl-1-propenone

Binding analysis and the ligand interaction of the compound 1-(4-nitrophenyl)-3-phenyl-1-propenone:
The binding analysis of this compound shows that, the compound is having two hydrogen bonding interaction with Val273 and Lys300. There is also a positive bonding interaction with Glu238. The bulky phenyl group is showing stacking interaction with Phe267. On closer analysis of the binding pattern of the compound reveals that, the carbonyl group has shifted slightly outside the active site pocket which impacts the lesser activity than other compounds. The binding analysis and the ligand interaction is shown in the figure 3. The docking score is tabulated in the table 1.

Binding analysis and the ligand interaction of the compound 1-(4-bromophenyl)-3-phenyl-1-propenone
The binding pattern of the compound 1-(4-bromophenyl)-3-phenyl-1-propenone shows that the compound is having four hydrogen bonding interactions. The phenoxy benzene group shows pi-positively charged interaction with Glu238. Also the Bromophenyl group is showing another pi-positively charged interaction with Lys300. Additionally the compound is having two hydrogen bonding interactions with Lys300 and Gln276. The binding analysis and the ligand interaction diagram is depicted in the figure 4 and the docking score is tabulated in the table 1.

Table:1. Docking score and Hydrogen bonding interactions for the synthesized compounds

S. No	Compound Name	Docking score	Ligand Interaction
1.	Reference Ligand	-6.39 kcal mol^{-1}	Asp271, Val273, Pro239, Gln274, Gly242, Glu238, Glu243
2.	1-(4-hydroxyphenyl)-3-phenyl1-1-propenone	-7.93 kcal mol^{-1}	Phe167, Gly242, Glu243, Glu238, Asp271, Thr275.
3.	1-(4-nitrophenyl)-3-phenyl-1-propenone	-7.02 kcal mol^{-1}	Glu238, Lys300, Phe267, Val273
4.	1-(4-bromophenyl)-3-phenyl-1-propenone	-6.71 kcal mol^{-1}	Glu238, Lys300, Gln274, Phe167

Figure 4: The binding analysis and the ligand interaction of the compound 1-(4-bromophenyl)-3-phenyl-1-propenone

CONCLUSION:

In conclusion, 30 mol% CAN supported HY-zeolite has been efficiently used as a catalyst for the oxidative condensation reaction of benzyl alcohol with substituted acetophenones in the presence of hydrogen peroxide as an oxidant in toluene to afford the corresponding chalcones in good to moderate yields. The compounds synthesized were redocked into the active site of the protein and the docking score of the reference ligand was found to be -6.39 kcal mol^{-1}. The carbonyl group (1) of the compound revealed a positive interaction with Asp271 and the carboxyl group shows the interaction with Gly242. The compound (2) has bulky group interaction with the aminoacid Phe167 and the positive interaction with the aminoacid Glu238. The Bromophenyl group is showing another pi-positively charged interaction with Lys300.

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